```
 s E2a

L3          442 E2A

=> s l1 and l3

L4          216 L1 AND L3

=> s E1

L5            1 "PAU LOUIS FRANCAIS"/IN

=> s (human embryonic retinoblast?)

         248743 HUMAN
           8262 EMBRYONIC
           1265 RETINOBLAST?
L6            8 (HUMAN EMBRYONIC RETINOBLAST?)
                (HUMAN(W)EMBRYONIC(W)RETINOBLAST?)

=> s l6 and l4

L7            5 L6 AND L4

=> d l7 1-5 ab bib


L7   ANSWER 1 OF 5  USPATFULL
AB     Presented are ways to address the problem of replication competent
      adenovirus in adenoviral production for use with, for example,
       gene therapy. Packaging cells having no overlapping sequences with a
       selected vector and are suited for large scale production of
recombinant
       adenoviruses. A method of the invention produces adenovirus
       incapable of replicating. The method includes a primary cell containing
       a nucleic acid based on or derived from adenovirus and an
       isolated recombinant nucleic acid molecule for transfer into the
primary
       cell. The isolated recombinant nucleic acid molecule is based on or
       derived from an adenovirus, and further has at least one
       functional encapsidating signal, and at least one functional Inverted
       Terminal Repeat. The isolated recombinant nucleic acid molecule lacks
       overlapping sequences with the nucleic acid of the cell. Otherwise, the
       overlapping sequences would enable homologous recombination leading to
       replication competent adenovirus in the primary cell into
       which the isolated recombinant nucleic acid molecule is to be
       transferred.
AN     2001:185090  USPATFULL
TI     Packaging systems for human recombinant adenovirus to be used
       in gene therapy
IN     Fallaux, Frits Jacobus, Leiderdorp, Netherlands
       Hoeben, Robert Cornelis, Leiden, Netherlands
       Van Der Eb, Alex Jan, Oegstgeest, Netherlands
       Bout, Abraham, Moerkapelle, Netherlands
       Valerio, Domenico, Leiden, Netherlands
PA     IntroGene B.V., Leiden, Netherlands (non-U.S. corporation)
       Rijksuniversiteit, Leiden, Netherlands (non-U.S. corporation)
PI     US 6306652          B1   20011023
AI     US 1999-333820           19990615 (9)
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RLI Continuation of Ser. No. US 1997-793170, filed on 25 Mar 1997, now patented, Pat. No. US 5994128 Continuation of Ser. No. WO 1996-NL244, filed on 14 Jun 1996
PRAI EP 1995-201611 19950615
EP 1995-201728 19950626
DT Utility
FS GRANTED
EXNAM Primary Examiner: Priebe, Scott D.; Assistant Examiner: Nguyen, Dave Trong
LREP Trask, Britt & Rossa
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 28 Drawing Figure(s); 27 Drawing Page(s)
LN.CNT 1883
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 2 OF 5 USPATFULL
AB The problem of replication competent **adenovirus** in virus production is solved in that we have developed packaging cells that have no overlapping sequences with a new basic vector and, thus, are suited for safe large scale production of recombinant adenoviruses. One of the additional problems associated with the use of recombinant **adenovirus** vectors is the host-defense reaction against treatment with **adenovirus**. Another aspect of the invention involves screening recombinant **adenovirus** vector lots, especially those intended for clinical use, for the presence of **adenovirus** E1 sequences, as this will reveal replication competent **adenovirus**, as well as revertant E1 adenoviruses. It is also an aspect of the present invention to molecularly characterize the revertants that are generated in the newer helper/vector combinations.
AN 2001:116818 USPATFULL
TI Packaging systems for human recombinant **adenovirus** to be used in gene therapy
IN Fallaux, Frits J., Leiderdorp, Netherlands
Hoeben, Robert C., Leiden, Netherlands
Bout, Abraham, Moerkapelle, Netherlands
Valerio, Domenico, Leiden, Netherlands
van der Eb, Alex J., Oegstgeest, Netherlands
Schouten, Govert, Leiden, Netherlands
PA Introgene B.V., Leiden, Netherlands (non-U.S. corporation)
PI US 6265212 B1 20010724
AI US 1999-356575 19990719 (9)
RLI Continuation-in-part of Ser. No. US 1997-793170, filed on 25 Mar 1997, now patented, Pat. No. US 5994128
PRAI EP 1995-201611 19950615
EP 1995-201728 19950626
DT Utility
FS GRANTED
EXNAM Primary Examiner: Clark, Deborah J. R.; Assistant Examiner: Wilson, Michael C.
LREP Trask Britt
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 21 Drawing Figure(s); 20 Drawing Page(s)
LN.CNT 2294
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 3 OF 5 USPATFULL
AB A method for intracellular amplification of DNA is disclosed. The method includes providing a mammalian cell with a first nucleic acid sequence encoding functional adenoviral **E2A** and E2B gene products and with a second nucleic acid sequence encoding a linear DNA fragment to be

amplified. The second nucleic acid sequence further has at least one functional adenoviral Inverted Terminal Repeat on a terminus and, in one embodiment where there is only a single ITR, a hairpin-like structure on the other terminus. This allows the linear DNA fragment to be acted upon by the adenoviral **E2A** and E2B gene products, thus intracellularly amplifying the linear DNA fragment, which can be extracted.

AN 2001:78920 USPATFULL
TI Method for intracellular DNA amplification
IN Hoeben, Robert Cornelis, Leiden, Netherlands
Bout, Abraham, Moerkapelle, Netherlands
PA Introgene B.V., Leiden, Netherlands (non-U.S. corporation)
PI US 6238893 B1 20010529
AI US 1999-334765 19990616 (9)
RLI Continuation of Ser. No. US 793170, now patented, Pat. No. US 5994128
PRAI EP 1995-201611 19950615
EP 1995-201728 19950626
DT Utility
FS Granted
EXNAM Primary Examiner: Schwartzman, Robert A.
LREP Trask Britt
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN 28 Drawing Figure(s); 27 Drawing Page(s)
LN.CNT 1908
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 4 OF 5 USPATFULL
AB The invention provides improved methods and products based on adenoviral materials which can advantageously be used in for instance gene therapy.

In one aspect an adenoviral vector is provided which has no overlap with a suitable packaging cell line which is another aspect of invention. This combination excludes the possibility of homologous recombination, thereby excluding the possibility of the formation of replication competent **adenovirus**. In another aspect an **adenovirus** based helper construct which by its size is incapable of being encapsidated. This helper virus can be transferred into any suitable host cell making it a packaging cell. Further a number of useful mutations to adenoviral based materials and combinations of such mutations are disclosed, which all have in common the safety of the methods and the products, in particular avoiding the production of replication competent **adenovirus** and/or interference with the immune system. Further a method of intracellular amplification is provided.

AN 2000:27804 USPATFULL
TI Packaging systems for human recombinant **adenovirus** to be used in gene therapy
IN Bout, Abraham, Ar Moerkapelle, Netherlands
Hoeben, Robert Cornelis, Ex Leiden, Netherlands
PA IntroGene, b.v., Netherlands (non-U.S. corporation)
PI US 6033908 20000307
AI US 1997-892873 19970715 (8)
RLI Continuation of Ser. No. US 793170
PRAI EP 1995-201611 19950615
EP 1995-201728 19950626
DT Utility
FS Granted
EXNAM Primary Examiner: Campell, Bruce R.; Assistant Examiner: Nguyen, Dave Trong

LREP Rae-Venter Law Group, P.C.
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 28 Drawing Figure(s); 27 Drawing Page(s)
LN.CNT 2015
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 5 OF 5 USPATFULL
AB Presented are ways to address the problem of replication competent **adenovirus** in adenoviral production for use with, for example, gene therapy. Packaging cells having no overlapping sequences with a selected vector and are suited for large scale production of recombinant adenoviruses. A system for use with the invention produces **adenovirus** incapable of replicating. The system includes a primary cell containing a nucleic acid based on or derived from **adenovirus** and an isolated recombinant nucleic acid molecule for transfer into the primary cell. The isolated recombinant nucleic acid molecule is based on or derived from an **adenovirus**, and further has at least one functional encapsidating signal, and at least one functional Inverted Terminal Repeat. The isolated recombinant nucleic acid molecule lacks overlapping sequences with the nucleic acid of the cell. Otherwise, the overlapping sequences would enable homologous recombination leading to replication competent **adenovirus** in the primary cell into which the isolated recombinant nucleic acid molecule is to be transferred.
AN 1999:155512 USPATFULL
TI Packaging systems for human recombinant **adenovirus** to be used in gene therapy
IN Fallaux, Frits Jacobus, Be Leiderdorp, Netherlands
Hoeben, Robert Cornelis, Ex Leiden, Netherlands
Van der Eb, Alex Jan, Tw Oegstgeest, Netherlands
Bout, Abraham, Ar Moerkapelle, Netherlands
Valerio, Domenico, Ez Leiden, Netherlands
PA IntroGene B.V., Leiden, Netherlands (non-U.S. corporation)
PI US 5994128 19991130
WO 9700326 19970103
AI US 1997-793170 19970325 (8)
WO 1996-NL244 19960614
19970325 PCT 371 date
19970325 PCT 102(e) date
PRAI EP 1995-201611 19950615
EP 1995-201728 19950626
DT Utility
FS Granted
EXNAM Primary Examiner: Campell, Bruce R.; Assistant Examiner: Nguyen, Dave Trong
LREP Trask, Britt & Rossa
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 21 Drawing Figure(s); 27 Drawing Page(s)
LN.CNT 2109
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> file biosis

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FULL ESTIMATED COST	20.00	20.15

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FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 5 December 2001 (20011205/ED)

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for details.

=> s E1

L8 0 "PAU LOUIS FRANCAIS"/IN

=> s l7

5046493 HUMAN
92192 EMBRYONIC
7849 RETINOBLAST?
3 (HUMAN EMBRYONIC RETINOBLAST?)
(HUMAN(W)EMBRYONIC(W)RETINOBLAST?)
22571 ADENOVIRUS
600 E2A
L9 0 L6 AND L4